Assessment of the risk of foodborne transmission and burden of hepatitis E in Switzerland

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Abstract: The objective of this study was i) to quantify the risk of hepatitis E for Swiss consumers by specified pork products and ii) to estimate the total burden of human food-borne hepatitis E in Switzerland. A quantitative risk assessment from slaughter to consumption was carried out according to the Codex Alimentarius framework. In the hazard characterization, assumptions were made due to the lack of a dose-response relationship for oral exposure to hepatitis E virus (HEV). The prevalence of HEV in 160 pig livers of 40 different Swiss fattening farms was examined and determined to be 1.3% (CI 0.3%; 4.4%). This result was used as input in the risk assessment model, together with data from other published studies. The annual burden of hepatitis E was estimated in terms of Disability Adjusted Life Years (DALY), using data about hepatitis E cases diagnosed between 2010 and 2015 at two major hospitals located in the canton Ticino. Only the risk of foodborne hepatitis E from products containing pork liver was evaluated, as those containing only pork meat could not be evaluated because of lack of data on HEV load in pork. Assuming that successful oral infection occurs in 1% of servings contaminated with high HEV loads (>105 genome copies), and that acute illness develops in 5% of susceptible consumers, the most likely annual number of foodborne hepatitis E cases in Switzerland was estimated to be 1481 (95% CI 552; 4488) if all products containing pork liver were considered. If only high-risk products, such as plain pork liver and liver sausages (e.g. Saucisse au Foie), were considered, the annual number of cases was estimated to be 176 (95% CI 64; 498). We were unable to calculate the total burden of hepatitis E in Switzerland due to lack of data. Yet, for the canton Ticino, it was shown that a significant increase had occurred from <5 DALY per 100,000 inhabitants before 2012 to >50 DALY per 100,000 inhabitants in 2015. This change could partly be due to an increased reporting and higher awareness among medical practitioners. Extrapolation to other regions could be accomplished if detailed information on food consumption patterns were available. Notification of HEV cases and attempts of cases source attribution would improve the basis for risk assessments.

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Title:

Assessment of the risk of foodborne transmission and burden of hepatitis E in Switzerland

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Abstract

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change could partly be due to an increased reporting and higher awareness among medical practitioners. Extrapolation to other regions could be accomplished if detailed information on food consumption patterns were available. Notification of HEV cases and attempts of cases source attribution would improve the basis for risk assessments.

Keywords

Pork; genotype 3 HEV; microbiological risk assessment; DALY

Highlights

- The prevalence of HEV RNA detection in Swiss pig livers at slaughter is 1.3% (95% CI 0.3%; 4.4%)
- The annual number of human hepatitis E cases due to high risk products was estimated as 176 (95% CI 64; 498)
- The total burden due to Hepatitis E in the canton *Ticino* was >50 DALY per 100,000 inhabitants in 2015

1. Introduction

Hepatitis E virus (HEV) is a relatively recently discovered hepatotropic virus (Reyes et al., 1991). To date, four genotypes (GT) affecting humans have been identified; GT3, and to a lesser extent GT4 represent the most common genotypes found in industrialized countries (Dalton et al., 2013). The clinical presentation is indistinguishable from Hepatitis A with classical symptoms including jaundice, anorexia, abdominal pain accompanied by fever, nausea and vomiting (Emerson and Purcell, 2003). Hepatitis E is usually self-limiting, but chronic infections have been described in immune-depressed patients (Bihl and Negro, 2009) and organ transplant recipients (Arends et al., 2014; Kamar et al., 2012). Fulminant and fatal HEV GT3 cases have also been reported in Europe and Japan, often in older males with underlying chronic liver diseases (Lewis et al., 2010). In pregnant women, the proportion of fulminant cases can reach 25%, although these cases were only described for GT1 strains circulating predominantly in developing countries (Smith, 2001).

While Hepatitis E was originally considered to be endemic only in areas of Asia, Africa and Mexico (WHO, 2010), sporadic cases were recently observed in developed countries, including Europe. These were initially considered to be imported, however, enhanced Hepatitis E surveillance has detected an increasing number of non-travel associated infections (Dalton et al., 2008), e.g. in France (Nicand et al., 2009), in the United Kingdom (Ijaz et al., 2014) and in Germany (Robert Koch Institut, 2015). The exact transmission routes for autochthonous HEV cases remain unknown, but foodborne transmission was identified as an emerging concern (EFSA, 2011). Contaminated products mostly include pork products (e.g. pork pies, under-cooked or

raw pork meat and liver pate), but also deer meat, wild boar meat, offal, shellfish and some ethnic foods are described (Lewis et al., 2010). Few outbreak investigations have been performed so far. Some of them confirmed the role of specific pork items such as *figatellu,* a traditional dried pig liver sausage widely eaten in France and commonly consumed raw (Colson et al., 2010), and undercooked pig liver–based stuffing (Guillois et al., 2015).

In Switzerland, no specific surveillance is in place and Hepatitis E is not a notifiable disease, therefore the exact number of diagnosed cases is not known (EDI, 2015). Few case reports confirmed that two autochthonous cases - including one acute case - with unknown exposure were diagnosed in the canton *Geneva* in 2004 (Sudre et al., 2005) and 12 acute autochthonous cases were diagnosed in the canton *Vaud* in 2013 (Hiroz et al., 2013). Recently, two acute cases were reported in the canton *Nidwalden* of a hunter who consumed deer and wild boar meat (Joller and Gaudenz, 2015), and in the canton *Saint Gallen* of a person who took part in a nature walk, during which wild, possibly contaminated herbs were collected and consumed (Sawatzki et al., 2015). One chronic case was also identified among a Swiss cohort of HIV patients (Kenfak-Foguena et al., 2011). However, Hepatitis E is likely to be underdiagnosed in Switzerland as the awareness for the disease is low among medical practitioners (Joller and Gaudenz, 2015). The occurrence of HEV is probably widespread as shown by a seroprevalence study conducted among blood donors in the Vaud canton (Kaufmann et al., 2011); depending on the diagnostic test used, the seroprevalence was estimated to be between 4.2% and 21.8% (Schnegg et al., 2013).

No quantitative data about the occurrence or the load of HEV in food is currently available in Switzerland. The seroprevalence of Hepatitis E in slaughtered pigs was estimated to be 49% at animal levels and 60% at farm level (Wacheck et al., 2012). A recent study covering the period of 2006-2011 confirmed HEV seroprevalence to be 58.1% in domestic pigs, and 12.5% in wild boars (Burri et al., 2014). The impact of this in terms of risk for the consumer of pork or wild boar is unknown.

In 2011, EFSA recommended to develop a risk assessment framework for specific HEV-commodity combinations and target populations, in order to identify specific data gaps, and to target research efforts (EFSA, 2011). In response to this recommendation we developed a population-based risk assessment framework for human Hepatitis E infection. More particularly, the specific study objectives were i) to assess the risk of hepatitis E from the consumption of pork and wild boar products, and ii) to estimate the overall burden of human hepatitis E in Switzerland.

2. Material and Methods

The quantitative risk assessment was carried out according to *Codex Alimentarius* Framework (Cac/Gl 63, 2007). Fig. 1 illustrates the framework of the risk assessment of hepatitis E infection by the consumption of pork and wild boar products.

[Fig. 1]

2.1. Hazard identification

HEV GT3 and GT4 are the genotypes considered as hazards in the present study, as foodborne transmission has been described for them (Berto et al., 2013; Borgen et al., 2008; Colson et al., 2012, 2010; Pavio et al., 2014). Current diagnostic methods are based on PCR methodology (Jothikumar et al., 2006; Mokhtari et al., 2013; Szabo et al., 2015; Ward et al., 2009). Accordingly, HEV RNA is the relevant unit of the hazard in the present analysis. It was assumed that products with high number of genome copies per gram (gc/g) were more likely to contain infectious HEV particles, potentially causing adverse health effect than those with lower ones.

In terms of relevant pork products, these were selected using the recipes of traditional pork products provided by the specialist school for butchers (http://www.abzspiez.ch/). Pork products were included if they contained pork liver and/or pork meat, and excluded if only containing pork fat. Fifty-two traditional meat products were included, pork meat, pork liver and wild boar liver. Products were grouped based on liver and meat content into three categories. Category 1 consisted of products containing pork liver in different proportions but no pork meat. It included products sold raw and cooked before consumption, such as pork and wild boar liver, as well as pasteurized products such as different liver paté´s. Category 2 consisted of products containing different proportions of pork liver and meat. Some, such as a cold smoked liver sausage, denominated *Saucisse au foie* are sold raw, to be cooked before consumption, others are sold pasteurized, such as *Paté de Campagne.* Category 3 included products containing pork meat but no liver, and which are either sold

pasteurized, such as ham, or sold raw to be cooked before consumption, such as pork meat.

2.2. Exposure assessment

2.2.1. Model frameworks

HEV contamination prevalence and load were initially modelled separately and then combined in the exposure assessment. Recipes and transformation processes were collected and their impact on HEV load and prevalence was modelled. The effects of salting, marinating, smoking, drying and curing were considered negligible, as HEV RNA has been found in dried cured sausages (Colson et al., 2010; Di Bartolo et al., 2012; Pavio et al., 2014). Only heat treatment, such as pasteurization or home cooking before consumption, was retained in the model. To quantify the impact of heat treatment, data on the decimal reduction time (D-value) and/or the effect of different time-temperature combinations on HEV load measured by current PCR tests were required but not available. The effect of heat on HEV load was estimated based on the findings of Barnaud et al. (2012) as described below. A mixing effect was ascribed to the fact that meat and liver from different carcasses are likely to be used for the preparation of transformed products, whereby a decrease in HEV RNA load (i.e. concentration of potential infectivity) would be expected due to dilution.

Finally, the level of HEV contamination at the point of consumption was estimated per serving of the specified pork product. An average serving size of 30 g was considered for sliced and spreadable pork products, and 150 g for large sausages (e.g. *Boudin*

179 *Blanc*, a sausage made of cooked meat and liver) and also for plain liver
180 (www.lebensmittelwissen.de). Cross-contamination of meat products by HEV
181 contaminated pork faeces, blood, liver, meat may occur at all steps along the
182 production chain, but were considered to be minor contributors to the overall model
183 outcome and therefore not considered further (Berto et al., 2012; Di Bartolo et al.,
184 2015).
185

186 **2.2.2. Parameter inputs**

187

188 HEV prevalence model

189 To investigate the prevalence of HEV in pig livers (P_{liver}) with a precision of 5% and a
190 confidence interval of 95%, 160 domestic pig livers originating from 40 herds were
191 sampled at a main Swiss slaughterhouse representative of approximately 50% of the
192 national pig slaughter volume. Sample size calculation was based on an expected HEV
193 prevalence in pig livers at slaughter of 5% (Berto et al., 2012; Bouwknegt et al., 2007;
194 Di Bartolo et al., 2012; Rose et al., 2011), a sensitivity of the diagnostic test of 0.9 and a
195 specificity of 0.99 (Hepatitis E Virus Detection Kit, Thermo Fisher Scientific) and
196 assuming an intra-cluster (i.e. intra-herd) correlation coefficient (ICC) of 0.2 (Dohoo et
197 al., 2009). Samples were handled as described by Rose et al., (2011): small liver
198 sections (2 cm x 1cm x 1cm) were cut from the left medial lobe of selected livers,
199 immediately placed at 4°C, frozen and stored at -80°C until further analysis. Gloves and
200 blades were changed between each liver to prevent any possible cross-contamination.
201 HEV was detected by real time PCR test using a commercial kit (Hepatitis E Virus
202 Detection Kit, Thermo Fisher Scientific) according to the protocol of the manufacture

on pools of four samples. Samples from positive pools were then tested individually, and the load of HEV in positive samples was estimated using the Hepatitis E quantification standard test (Thermo Fisher Scientific).

The output of the prevalence model was the proportion of HEV contamination in the specified categories of products, estimated as follows:

$$P_{product} = 1-[(1-P_{liver})(1- P_{meat})] \quad \text{(Eq. 1)}$$

where $P_{product}$ represents the prevalence of HEV RNA-contaminated specified pork products at the point of consumption. P_{liver} and P_{meat} represent the prevalence of HEV RNA positive pork liver and meat at slaughter, respectively. $P_{wildboar}$ was used instead of P_{liver} to represent the prevalence of HEV contamination in wild boar liver. No data was available of the prevalence of HEV contaminated wild boar meat. The model parameters are shown in Table 1.

Table 1

Input parameters of the exposure assessment models of foodborne Hepatitis E and the Hepatitis E DALY model.

HEV Prevalence Model				HEV Load Model				DALY Model			
Parameter Prevalence Model	Deterministic (number positive/ number tested)	Probability distribution of input parameters	References Prevalence Model	**Parameter Load Model**	Probability distributions and input parameters	References Load Model	Assumptions DALY Model	**Parameter DALY Model**	Outcome 1	Outcome 2	Source
HEV prevalence in pig liver (P_{liver})	0.034 (136/4027)	Beta (137, 3892)*	(Berto et al., 2012; Di Bartolo et al., 2012; Rose et al., 2011), own data	**Log HEV RNA concentration in liver (C_{liver})**	Lognormal (6.11, 1.116)	(Barnaud et al., 2012; Leblanc et al., 2010; Pavio et al., 2014; Wilhelm et al., 2014; Yazaki et al., 2003) and own data	mean = geometric mean of maximum HEV RNA loads, std = std of max loads	**Age at onset in male patients (years)**	Beta Pert (24, 57, 93)	Beta Pert (38, 68, 88)	*Ticino* data (own data)
HEV prevalence in wild boar liver ($P_{wildboar}$)	0.184 (42/228)	Beta (43, 187)	(Mesquita et al., 2014; Schielke et al., 2009)	**Log HEV RNA load in pork meat/chops**	none	(Leblanc et al., 2010; Wilhelm et al., 2014)	Below threshold, assume "very low load"	**Age at onset in female patients (years)**	Beta Pert (32, 47, 82)	Beta Pert (34, 82, 90)	*Ticino* data (own data)
HEV prevalence in pig meat (P_{meat})	0.012 (9/765)	Beta (10, 757)	(Berto et al., 2012; Di Bartolo et al., 2012; Leblanc et al., 2010; Wilhelm et al., 2014)	**Mixing effect (Mix_{Load})**	Pert (-3.237, 1.071, 4.372)	(ANSES, 2015; Leblanc et al., 2010; Pavio et al., 2014; Renou et al., 2014; Wilhelm et	Composition of dried pork liver sausages: 40% liver	**Outcome duration (years)**	Beta Pert (0.08, 0.11, 0.15)	Beta Pert (0.08, 0.11, 0.15)	(Kamar et al., 2012)

				al., 2014)				
	Heat reduction (HR_{load})	Pert (2.282, 2.609, 2.935)	(Barnaud et al., 2012)	Heating at 68°C and 71°C during 5 min	**Age at death in male patients (years)**	Beta Pert (61, 70, 80)	Beta Pert (39, 67, 68)	*Ticino* data (own data)
					Age at death in female patients (years)	-**	Beta Pert (71, 82, 83)	*Ticino* data (own data)
					Disability weight w_i	0.058	0.353	(Havelaar et al., 2012)

223

224 HEV load model

225 The output of the HEV RNA load model was the concentration of HEV RNA throughout
226 the different processing steps until the point of consumption. The concentration of
227 HEV in the product at consumption ($C_{product}$), expressed as log genome copies per gram
228 (gc/g):

229 $C_{product} = (L*C_{liver}) - Mix_{Load} - HR_{load}$ (Eq. 2)

230

231 Where C_{liver} represents the log HEV concentration in positive pig livers, modelled using
232 own data and according to published maximum log HEV loads (Barnaud et al., 2012;
233 Leblanc et al., 2010; Pavio et al., 2014; Wilhelm et al., 2014; Yazaki et al., 2003). No
234 values of HEV RNA load of pork meat were available (Leblanc et al., 2010; Wilhelm et
235 al., 2014). Products containing only pig meat but no liver were therefore considered to
236 have loads below $<10^3$ gc/g, i.e. below PCR detection threshold (Leblanc et al., 2010;
237 Wilhelm et al., 2014), and not further considered in the HEV load model. *L* represents
238 the proportion of pork liver in the product. Mix_{Load} *and* HR_{load} represent the log HEV
239 RNA load reduction (gc/g) in the product due to mixing with other ingredients and due
240 to heat processing (pasteurization or cooking), respectively. Model parameters are
241 shown in Table 1.

242

243 The effect of mixing HEV contaminated with uncontaminated pork ingredients (Mix_{Load})
244 on the HEV load of the final product was estimated by comparing the virus load
245 expected according to the model with that observed in dried pork liver sausages at

246 retail (Pavio et al., 2014; Renou et al., 2014). It was assumed that dried liver sausages
247 were composed of 40% pork liver.
248
249 The effect of pasteurization on HEV RNA load (HR_{load}) was modelled by a Pert
250 distribution using information on the effect of heating HEV contaminated material
251 during 5 minutes at 68°C and at 71°C (Barnaud et al., 2012). The log HEV
252 concentration per serving of specified product ($C_{serving}$), expressed as (gc/serving), was
253 calculated:
254 $C_{serving} = C_{product} + log\ S$ (Eq. 3)
255
256 Where $C_{product}$ represents the log HEV concentration per gram of the specified product
257 (gc/g) and S represents the average serving size in gram (g) of the product.
258
259 To quantify both exposure and load, two stochastic Monte Carlo risk assessment
260 models were developed using the software @RISK for EXCEL version 6.2.0 (Palisade
261 Corporation 2013). Latin hypercube sampling of the distributions was performed by
262 10,000 iterations.
263

264 **2.3. Hazard characterization**

265 For the hazard characterization the prevalence and load models of the exposure
266 assessment were combined. A dose-response relationship for oral exposure to
267 hepatitis E virus was not available and therefore needed to be approximated. A
268 threshold dose of 10^5 gc per serving was assumed to represent the minimum dose
269 potentially resulting in infection by the oral route (AFFSA, 2009; Renou et al., 2014).

This represents a value between the reported effective dosis of $10^{4.68}$ gc/g (Renou et al., 2014) and an estimated 50% oral infectious dose of $10^{5.5}$ genome equivalents (AFFSA, 2009). The proportion of infections resulting in acute disease and medical attention seeking is unknown (Aggarwal, 2011). The probability that consumption of any random serving of pork product leads to acute illness (P_{acute}) was estimated:

$$P_{acute} = P_{product} * P_{hi} * P_{inf} * P_{ill} \quad \text{(Eq. 4)}$$

Where $P_{product}$ is the probability of HEV contaminated specified pork product (Prevalence model, Eq. 1). P_{hi} corresponds to the probability of the contaminated products containing HEV RNA levels >10^5 gc /serving, and was read off the distribution curve of the load model. P_{inf} is the probability of successful infections upon oral exposure to doses higher than the threshold. To reflect uncertainty and partially effective heat treatment, it was assumed that products containing pork liver and high HEV loads may, despite pasteurization or cooking, contain approximately 1% of infectious HEV (Pert 0.005, 0.01, 0.02). P_{ill} is the probability of acute illness after infection in the susceptible population. The latter was modelled by a Pert distribution. The maximum value of 0.14 was derived from foodborne outbreaks, where only the index cases seeking medical attention (7/50) were considered (Colson et al., 2010; Guillois et al., 2015; Said et al., 2009). The minimum and most likely values for the probability of developing acute illness after infection were assumed to be 0.01 and 0.05, respectively. Other outcomes, such as asymptomatic, mild clinical and chronic infection were not considered.

2.4. Risk characterization

294 The expected number of acute illness cases caused by foodborne hepatitis E infection
295 in Switzerland were estimated based on meat consumption data of 2012 (BAG, 2012)
296 and on population demographics of 2014 (http://www.bfs.admin.ch/). In Switzerland,
297 the average annual consumption of meat was of 51.98 kg per person, consisting of
298 6.64 kg (14%) pork meat and of 16.84 kg (35.5%) of meat products such as charcuterie
299 and sausages (Proviande, 2013). As consumption data for specific pork products was
300 not available, we assumed that the list of 52 pork products (i.e. excluding pork meat)
301 included in our study was comprehensive, and that every adult inhabitant consumed
302 all the 50 selected Swiss traditional pork products, as well as pork liver and wild boar
303 liver, in equal proportions, up to the average of 16.84 kg per year, resulting in an
304 average (rounded) annual consumption of 300 g of each product. The risk
305 characterization focussed exclusively on products containing pork liver.
306
307 Data on population demographics in Switzerland were derived from the interactive
308 database STAT-TAB of the Swiss Federal Statistical Office (http://www.bfs.admin.ch/).
309 The target population of pork consuming adult permanent residents was calculated as
310 6,113,400, i.e. excluding 3% of vegetarians (http://www.swissveg.ch) as well as adult
311 muslim residents (STAT-TAB). It was assumed that seropositivity confers immunity to
312 HEV reinfection (Arends et al., 2014; Said et al., 2009). The susceptible population
313 (*Pop*) corrected by the HEV seroprevalence, which was modelled as Uniform
314 distribution (0.04, 0.22) (Schnegg et al., 2013). The total number of expected cases of
315 acute hepatitis E per year in Switzerland was therefore:
316 $N_{cases} = Pop * P_{acute} * \sum_i N_{serv(i)}$ (Eq. 5)
317

Where P_{acute} is the probability that consumption of any random serving of pork product leads to acute illness (Eq. 4), *Pop* is the susceptible adult permanent resident population and $N_{serv(i)}$ is the number of servings of each product (*i*) consumed annually.

Two scenarios were created to estimate the number of annual cases due to foodborne hepatitis E. Scenario 1 assumed that around 1% of infectious HEV (P_{inf} = Pert 0.005, 0.01, 0.02) may occur in all pork liver containing products, including those pasteurized before retail. Scenario 2 assumed that 1% of infectious HEV (P_{inf} = Pert 0.005, 0.01, 0.02) is only observed in "high risk products", which are those sold raw and inadequately cooked before consumption.

Sensitivity analysis was conducted in @RISK for EXCEL version 6.2.0 to identify the model input parameters mostly influencing the outcomes of the risk characterization.

2.5. Estimation of the burden of hepatitis E

The burden of hepatitis E in Switzerland was estimated in terms of Disability Adjusted Life Years (DALY) (Murray et al., 2012). DALY were calculated from the sum of the number of years of life lost due to the mortality of hepatitis E (YLL) and the number of years lived with a disability (YLD):

$$DALY = YLL + YLD \quad \text{(Eq. 6)}$$

with $$YLL = \sum_i d_i * e_i \quad \text{(Eq. 7)}$$

where d_i corresponds to the number of fatal cases due to health outcome i and e_i to the expected individual live span at the age of death, and:

342 $YLD = \sum_i n_i * t_i * w_i$ (Eq. 8)

343

344 where n_i represents the number of cases with health outcome *i*, t_i the duration of the
345 health outcome i (in years) and w_i the disability weight assigned to health outcome *i*
346 that ranges between 0 (perfect health) and 1 (equivalent to death).

347

348 Because hepatitis E is not notifiable in Switzerland, the 33 major accredited diagnostic
349 laboratories (i.e. cantonal hospital laboratories or private laboratories) were contacted
350 to provide data (Federal Office of Public Health, 2015). No authorization was required
351 as only anonymous, non-genetic data were requested, with no possibility to assign the
352 data to a specific person (Swiss Federal Council, 2011). Six laboratories confirmed that
353 they were performing hepatitis E diagnosis, while 13 laboratories were transferring
354 their samples to bigger laboratories for diagnosis. Thus, DALY calculations were
355 performed using the data from two hospitals, located in the canton of *Ticino* and
356 believed to centralize all hepatitis E cases from the *Ticino* reference population.

357

358 Hepatitis E cases were defined as patients showing alanine aminotransferase (ALT) and
359 aspartate aminotransferase (AST) elevation and hepatitis E IgG or IgM positive
360 serology. As only acute hepatitis E cases (i.e. self-limited hepatitis E with ALT and AST
361 elevation during 4 to 6 weeks) had been diagnosed at the two *Ticino* hospitals, chronic
362 cases were excluded from further DALY calculations. PCR testing was also not
363 considered as it is not performed systematically in Switzerland, and because the short
364 RNA detection window might lead to false negative results (Kamar et al., 2014). Total
365 number of cases was collected for the period from January 1st, 2010 to September 1st,

2015. Laboratory and clinical records were consulted by hospital personnel in order to collect, for each individual case, the diagnostic year, IgG and IgM serological test outcomes, patient sex and age at the moment of diagnosis, possible route of infection (i.e. travel- or meat consumption related), presence of underlying chronic disease or immunosuppression, and hepatitis E outcome. Data on the serological test´s diagnostic sensitivity and specificity were also collected for the period under study.

In accordance with Havelaar et al. (2012), two disease outcomes were considered: 1) hepatitis with general practitioner (GP) visit but no hospitalization (i.e. mild hepatitis E) and 2) hepatitis with hospitalization (i.e. severe hepatitis E). Cases not visiting their GP were not considered. Annual DALY estimates were calculated for 2010-2015. Certain model parameters changed over the years, namely: the number of fatal cases and the number of cases with outcomes 1 and 2. Other parameters were fixed over the years as described in Table 1. The canton *Ticino* population data by sex and age categories, as well as life expectancy data were obtained from the Swiss national statistics (http://www.bfs.admin.ch/). DALY calculations were conducted in R 3.0.1 using the DALY package. No age weighting or discount rate was applied.

3. Results

3.1. Exposure assessment

Out of 160 pig livers of 40 different Swiss fattening farms, two yielded a positive result, with a HEV load of $10^{2.033}$ and $10^{4.047}$gc/g. The prevalence was therefore established to be

1.25 % (95% CI 0.3%; 4.4%). The highest prevalence of HEV contamination was estimated as 18.38% (95% CI 13.93%; 23.97%) for wild boar liver or products thereof (category 1). The HEV prevalence of other category 1 products consisting of pork liver was estimated as 3.37% (95% CI 2.86%; 3.98%) (Appendix Table A. 1. and Fig. A. 1.). Products containing pork meat and pork liver (category 2) and those containing pork meat but no liver (category 3), had an estimated HEV prevalence of 4.60% (95% CI 3.80%; 5.72%) and 1.19% (95% CI 0.62%; 2.21%), respectively.

HEV contamination load was estimated only for products containing pork liver (categories 1 and 2), (Appendix Table A. 1. and Fig. A. 2.). Eight meat products plus plain liver were retained in the model. The highest estimated log HEV contamination level was 3.5 gc/g (95% CI 1.6; 6.0) for cooked pork liver. The lowest expected log HEV load of 1.6 gc/g was estimated to occur in *Saucisse au Foie* (95% CI -2.0; 5.0). The log HEV load of the remaining products, which include diverse liver paté´s and terrines ranged from 2.3 (95% CI -1.2; 5.7) in *Paté au foie* to 1.9 (95% CI -1.7; 5.3) in *Hausmacherleberwurst*.

3.2. Hazard characterisation

The estimated overall probabilities of any random serving of different products being contaminated above the hypothetical oral infection threshold of 10^5 gc in pasteurized products ranged from a maximum of 1.33% in a 150g serving of *Leberwurst Boudin Blanc*, to 0.51% (95% CI 0.43%; 0.60%) in *Hausmacherleberwurst*, a pasteurized spreadable liver paté (Appendix Table A. 1. and Fig. A. 3.). In the “high risk” products, which are those sold raw to be cooked before consumption, the estimated

probabilities of high load HEV contamination were 2.40% (95%CI 2.04%; 2.83%) in random servings of 150g of pork liver, and 0.96% (95% 0.79%; 1.17%) in 150g of *Saucisse au foie*.

The most likely number of cases of acute illness arising per 100,000 random servings of the specified pork liver-containing products ranged between a maximum of 1.10 (95% CI 0.43; 3.36) in pork liver and a minimum of 0.27 (95% CI 0.09; 0.71) in *Hausmacherleberwurst* (Appendix Table A. 1. and Fig. A. 4.).

3.3. Risk characterisation

As the estimated average annual consumption of individual pork products was estimated as (rounded) 300 g per person, we considered an annual consumption of two servings per person for products with serving sizes of 150 g (*Saucisse au Foie*, *Leberwurst Boudin blanc* and pork liver) and ten servings of each product of 30 g serving size.

The most likely annual number of foodborne cases of hepatitis E per year in Switzerland according to scenario 1, was estimated to be 1,481 (95% CI 552; 4,488) (Appendix Table A. 1. and Fig. A. 5.). Of these, the consumption of *Terrine du Chef* and *Paté de Campagne*, both pasteurized products, was estimated to result in the highest number of annual cases (220, 95% CI 83; 658). All other products contributed less to the annual number of acute hepatitis E cases. Scenario 2 took into consideration only non-pasteurized products, i.e. those sold raw and potentially inadequately cooked by the consumer. According to this scenario, pig liver and S*aucisse au foie* were considered such “high risk products”, and estimated to result in 129 (95% CI 46; 355)

438 and 47 (95% CI 18; 143) annual cases of hepatitis E, respectively. Thus, the total annual
439 number of foodborne hepatitis E cases according to scenario 2 was estimated as 176
440 (95% CI 64; 498).
441
442 Sensitivity analysis showed that the estimated number of hepatitis E cases per year in
443 Switzerland was mostly influenced by the proportion of acute illness upon infection
444 (P_{ill}), the proportion of successful infections upon oral exposure to high HEV doses
445 (P_{inf}), the prevalence of HEV in pig livers, HEV seroprevalence in the human population
446 and HEV prevalence in pork meat (Appendix Table A. 2.).
447

448 **3.4. Estimated burden from Hepatitis E in the canton *Ticino* of Switzerland**

449 A total of 119 hepatitis E cases were diagnosed at the two hospitals of the canton
450 *Ticino* between January 1st, 2010 and September 1st, 2015, among which 35 required
451 hospitalization and 9 had a fatal outcome (Appendix Table A. 3.). Cases were mostly
452 observed in males (68%) at a median age of 57 years old for cases visiting their GP and
453 68 years old for hospitalized cases.
454
455 The number of diagnosed cases substantially increased between 2012 (n=3 cases) and
456 2015 (n=51 cases for the 8-month period), leading to an increase in mean DALY per
457 year and per 100,000 inhabitants (Table 2).
458
459

Table 2

Burden of Hepatitis E in the canton *Ticino* between 2010 and 2015.

Year	Mean YLL per year (CI 95%)*	Mean YLD per year (CI 95%)	Mean DALY per year (CI 95%)	Mean DALY per 100,000 inhabitants (CI 95%)
2010	10.30 (5.09; 15.47)	0.06 (0.05; 0.07)	10.36 (5.14; 15.52)	3.10 (1.54; 4.65)
2011	0.00 (0.00; 0.00)	0.07 (0.06; 0.07)	0.07 (0.06; 0.07)	0.02 (0.02; 0.02)
2012	0.00 (0.00; 0.00)	0.02 (0.02; 0.02)	0.02 (0.02; 0.02)	0.01 (0.01; 0.01)
2013	17.97 (12.70; 27.80)	0.45 (0.38; 0.52)	18.41 (13.17; 28.26)	5.31 (3.80; 8.15)
2014	40.54 (29.09; 60.38)	0.59 (0.51; 0.67)	41.12 (29.68; 60.96)	11.74 (8.47; 17.40)
2015 (up to 01/09/15)	170.04 (165.22; 177.80)	0.73 (0.63; 0.82)	170.77 (166.02; 178.55)	48.74 (47.39; 50.96)

*95% Credibility interval

4. Discussion

The exposure assessment showed that HEV prevalence in Swiss pork livers was slightly lower, but still within the range of prevalence described in other European countries (Berto et al., 2012; Bouwknegt et al., 2007; Di Bartolo et al., 2012). At retail, we estimated that < 6% of the products containing pork liver (categories 1 and 2), and < 3% of the products containing pork meat could be contaminated with HEV genetic material. These values are below the range of 6% to 22% recently described in pork sausages with and without liver in Europe (Berto et al., 2012; Di Bartolo et al., 2015, 2012; Szabo et al., 2015). Regarding viral load in pork products at retail, our estimates of log HEV load at consumption, ranging between 3.5 (95% CI 1.6; 6.0) and 1.6 (95% CI 2.0; 5.0) gc/g, were slightly lower than those described in dried and fresh liver

476 sausages, where log loads of up to 6 were measured (Colson et al., 2010; Pavio et al.,
477 2014). These discrepancies between estimated and published HEV prevalence and load
478 values in pork products may be explained by the input parameters of the prevalence
479 model, as HEV prevalence data may vary geographically according to pig husbandry
480 practices. Further, the sensitivity of current PCR methodologies varies and is
481 influenced by DNA extraction methods; and current PCR methods are unable to
482 discriminate between infectious and inactivated HEV particles (Baylis et al., 2011;
483 Jothikumar et al., 2006; Mokhtari et al., 2013; Szabo et al., 2015; Ward et al., 2009).
484 This may over- or underestimate HEV prevalence and load in pork products and may
485 explain the discrepancy between our model´s results and those of other studies (Berto
486 et al., 2012; Colson et al., 2010; Di Bartolo et al., 2015, 2012; Szabo et al., 2015). To
487 improve accuracy of data for risk assessments, internationally standardized HEV PCR
488 assays are needed, that specifically target infectious virus (Baylis et al., 2013, 2011;
489 EFSA, 2011; Szabo et al., 2015). A promising PCR assay which targets amplification of
490 RNA of intact viral particles has been described recently (Schielke et al., 2011). The
491 underlying assumption is that only intact viral particles are infectious, whereas viral
492 RNA fragments that may be amplified by PCR are not. This assay however requires
493 further validation regarding the correlation of PCR signals with HEV infectivity. Further
494 applications of such assays would be to assess the effect of heat treatment (D-values)
495 and other processing steps on HEV prevalence and load in meat products.
496
497 The hazard characterization was based on major assumptions related to the dose-
498 response relationship. The proportion of consumers getting successfully infected after
499 oral exposure (P_{inf}) to a given HEV threshold dose (10^5 g.c.), and the proportion of

500 those infected that develop severe acute illness (P_{ill}) are unknown for foodborne
501 Hepatitis E (EFSA, 2011). Model parameters were approximated from previously
502 published data (AFFSA, 2009; Colson et al., 2010; Guillois et al., 2015; Renou et al.,
503 2014; Said et al., 2009). Hepatitis E dose-response is very likely to vary individually,
504 especially if co-morbidities such as pre-existing liver disease are present (EFSA, 2011;
505 Kamar et al., 2012). The proportion of successful infections upon oral exposure to high
506 HEV doses and the proportion of acute illness upon infection should be better
507 informed as these mostly influence the model outcomes.
508
509 The risk characterization was based on average meat consumption and population
510 demographics. However, individual tastes, cooking habits, gender, socio-economic
511 background and other factors are very likely to influence meat consumption and hence
512 the risk of contracting HEV infection and of developing acute disease (EFSA, 2011;
513 Kamar et al., 2012). These should be included in future risk assessments.
514
515 The risk of foodborne hepatitis E was characterized initially (scenario 1) considering all
516 pork products containing liver, regardless of whether they were pasteurized, resulting
517 in a most likely annual number of 1,481 cases (95% CI 552; 4,488), or an incidence rate
518 of 16.87 (95% CI 7.54; 58.94) per 100,000 inhabitants. Scenario 2 assumed that HEV
519 was totally inactivated in pasteurized products and the model only included “high risk
520 liver products”, resulting in a total of 176 (95% CI 64, 498) cases, or an incidence rate
521 of 2.17 (95% CI 0.97, 7.60) per 100,000 inhabitants (Appendix Table A. 1. and Fig. A. 6.).
522 Repeated exposure was not considered; patients in the incubation period (estimated
523 to be 40 days on average) (WHO, 2015) were not removed from the population at risk.

524

525 In 2014, the incidence rate of hepatitis E in the canton of Ticino was calculated to be
526 12 cases per 100,000 inhabitants (Appendix Table A. 3.). Despite being clearly below
527 this value, we consider the estimate of the Scenario 2 to be more realistic than that of
528 Scenario 1. Other food items such as partially uncooked pork, wild boar and deer meat,
529 various types of sausages including fermented sausages may account for the remaining
530 difference of observed cases (Di Bartolo et al., 2012; Schielke et al., 2009; Tei et al.,
531 2003). These products were not included in our risk assessment due to missing data
532 and a lack of evidence of outbreaks associated with meat (Colson et al., 2010; Guillois
533 et al., 2015; Renou et al., 2014).

534

535 Also, cases recorded in the canton *Ticino* included all hepatitis E cases, with almost no
536 information about possible exposure routes. Source attribution of Swiss hepatitis E
537 cases needs to be further explored. An expert elicitation conducted in the Netherlands
538 concluded that on average, hepatitis E was transmitted at 14% by food, 25% by the
539 environment, 8% via human to human transmission, 11% from direct contact with
540 animals and 43% during foreign travel by any of the above pathways (Havelaar et al.,
541 2008). Yet, this elicitation was based on only two experts, and confidence intervals
542 were broad. A study conducted in the canton *Zurich* of Switzerland showed no
543 increased risk of HEV infection in workers exposed to sewage (Jeggli, 2004), and no
544 HEV was detected in effluent samples from *Zurich* water treatment plants (Masclaux et
545 al., 2013). Moreover, using sewage sludge from water treatment plant as fertilizer in
546 agriculture is banned in Switzerland since 2006 (Swiss Federal Office for the
547 Environment, 2006). So transmission from the environment seems very unlikely.

548

549 The hypothesis of a transmission by direct contact with animals is likely among certain
550 occupational groups such as pig veterinarians (Bouwknegt et al., 2008; Meng et al.,
551 2002), pig farmers (Christensen et al., 2014; Galiana et al., 2008) and abattoir
552 personnel (Vulcano et al., 2007). However to our knowledge, no study has shown that
553 the occurrence of symptomatic cases was more frequent in these groups. Direct
554 human-to-human transmission could also occur via blood transfusion in Switzerland, as
555 4.2% to 21.8% of blood donors in the canton Vaud were shown to be IgG seropositive
556 (Schnegg et al., 2013). However, the proportion of seropositive donors carrying HEV in
557 their blood is unknown. More detailed investigation of cases would help rank the
558 relative importance of the different transmission pathways, and support the
559 prioritization of future preventive measures.

560

561 The study of the burden of hepatitis E in Switzerland highlighted a substantial increase
562 in mean DALY between 2012 and 2015; a recent increase in Hepatitis E incidence was
563 also described in other European countries, e.g. France (Lhomme et al., 2015),
564 Germany (Robert Koch Institut, 2015) and England (PHE, 2015). We estimated
565 Hepatitis E burden in *Ticino* for 2013 to be 5.31 (95% CI 3.80, 8.15) per 100,000
566 inhabitants in Ticino. For the same year, the burden of hepatitis A, human tuberculosis
567 and diarrheal diseases in Switzerland was estimated to be 4.07 (95% CI 2.59, 5.94),
568 16.35 (95% CI 13.86, 20.50) and 25.02 (95% CI 20.79, 29.91) per 100,000 inhabitants,
569 respectively (IHME, 2015). Years of life lost (YLL) was the major contributor to the total
570 hepatitis E burden; this is related to the acute clinical presentation of the disease.

571

572 However, in accordance with Kamar et al. (2012), several reasons could have led to
573 underestimating the burden of hepatitis E in Switzerland (Kamar et al., 2012). First,
574 Swiss medical practitioners appear to be little aware of the disease (Joller and
575 Gaudenz, 2015). Yet, the situation has improved in the recent years, as demonstrated
576 by the increasing demand for hepatitis E serology testing (Lausanne University
577 Hospital, Division of Immunology and Allergy, personal communication). Additionally,
578 acute hepatitis E due to HEV GT 3 was shown to be
579 misdiagnosed; it was mistaken for drug-induced liver injury in six (13%) of 47 patients
580 in the UK (Dalton et al., 2007) and nine (3%) of 318 cases in the US (Davern et al.,
581 2011). The fact that the present study did not include cases not visiting their GP and
582 chronic cases could also have resulted in underestimating the total burden of hepatitis
583 E, but the impact of these cases was considered to be very low.
584
585 DALY calculations were based on data from a single canton representing 4.3% of the
586 Swiss population in 2014, as no access to hepatitis E patients' data was available in
587 other cantons. Making hepatitis E a notifiable disease in Switzerland would certainly
588 help get a better estimate of the national burden. Extrapolations of *Ticino* DALY
589 estimates to other cantons should be made with caution, as populations from other
590 cantons might have other food consumptions or travel habits.
591
592 We conclude that the burden of hepatitis E is low in Switzerland but an apparent
593 increasing trend deserves attention. Source attribution would allow assessing the
594 importance of foodborne exposure compared to other exposure routes, yet, the
595 relative contribution of meat consumption is expected to remain non-negligible. Pork

596 and wild boar products containing liver and sold raw were identified as the highest-risk
597 products. Future risk management options might include providing information to the
598 consumers. Making hepatitis E a notifiable disease is a requirement for further health
599 impact assessments. In accordance with Bijkerk et al. (2015), the workload of case
600 reporting programmes needs to be balanced against expected public health benefits.
601

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609

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APPENDIX A – Supporting material

Table A. 1.

Risk assessment for foodborne Hepatitis E: Results of the exposure assessment for Swiss traditional pork products (mode and 95% CI).

PRODUCT CATEGORY	Pork liver content	PRODUCT*) (serving size)	HEV RNA prevalence (%) (2.5th and 97.5th percentiles = 95% CI)	HEV RNA load (log gc/g) (2.5th and 97.5th percentiles = 95% CI)	Probability (%) random serving HEV load >10^5gc (2.5th and 97.5th percentiles = 95% CI)	Hazard characterization (Number of cases/100,000 servings)	Risk characterization (Number of cases per year in Switzerland)	Incidence rate per 100,000 inhabitants (2.5th and 97.5th percentiles = 95% CI)
1- Pork liver (n=6)	100%	Pork liver (150g)	3.37 (2.86, 3.98)	3.45 (1.59, 5.97)	2.40 (2.04, 2.83)	1.10 (0.43, 3.36)	129 (46, 355)	1.93 (0.69, 5.41)
	100%	Wild boar liver (150g)	18.38 (13.93, 23.97)	Likely similar to pork, (no load info available)	Not determined	Not determined	Not determined	Not determined
	30%	*Pâté au foie* (Grundbrät) (30g)	3.37 (2.86, 3.98)	2.34 (-1.23, 5.73)	0.73 (0.63, 0.87)	0.39 (0.13, 1.03)	199 (70, 546)	2.96 (1.07, 8.32)
	25%	*Streichleberwurst* (30g)	3.37 (2.86, 3.98)	2.26 (-1.31, 5.65)	0.70 (0.59, 0.82)	0.37 (0.12, 0.98)	188 (66, 517)	2.8 (1.01, 7.87)
	15%	*Geflügelfleischterrine* (30g)	3.37 (2.86, 3.98)	2.04 (-1.53, 5.43)	0.59 (0.50, 0.69)	0.31 (0.10, 0.82)	158 (56, 434)	2.35 (0.85, 6.61)
	10%	*Hausmacherleberwurst* (30g)	3.37 (2.86, 3.98)	1.86 (-1.71, 5.26)	0.51 (0.43, 0.60)	0.27 (0.09, 0.71)	136 (48, 374)	2.03 (0.73, 5.70)
2- Pork liver and meat (n=4)	20%	*Pâté de Campagne* (30g)	4.60 (3.80, 5.72)	2.16 (-1.41, 5.56)	0.88 (0.72, 1.09)	0.36 (0.16, 1.23)	219 (83, 658)	3.87 (1.26, 10.08)
	20%	*Terrine du Chef* (30g)	4.60 (3.80, 5.72)	2.16 (-1.41, 5.56)	0.88 (0.72, 1.08)	0.36 (0.16, 1.23)	220 (83, 658)	3.87 (1.26, 10.08)
	15%	*Leberwurst - Boudin blanc* (150g)	4.60 (3.80, 5.72)	2.04 (-1.53, 5.43)	1.33 (1.09, 1.64)	0.54 (0.24, 1.85)	66 (25, 198)	1.17 (0.38, 3.04)
	5%	*Saucisse au foie* (150g)	4.60 (3.80, 5.72)	1.56 (-2,01, 4.96)	0.96 (0.79, 1.17)	0.38 (0.17, 1.33)	47 (18, 143)	0.84 (0.27, 2.19)
3- Pork meat (n=43)	0%	Pork meat	1.19 (0.62, 2.21)	Not determined, likely <1	Not determined	Not determined	Not determined	Not determined
	0%	*Saucisse aux choux (Kabiswurst), Saucisson, Zwiebelmettwurst,*	1.19 (0.62, 2.21)	Not determined, likely <1	Not determined	Not determined	Not determined	Not determined

		Schweizer Salami, Salami nach Bauernart, Knoblauchwurst, Salsiz, Rauchwurst, Bündner Beinwurst, Bauernschüblig, Walliser Hauswurst, Rauchsalami, Saucisse d'Ajoie, Pantli, Alpenklubler, Touristenwurst,Schweinsbratwurst, Luganighe, Zampone, Frankfurterli, Cotechini, Longeole, Engadiner, Glarner Kälberwurst, Hallauer Schinkenwurst, Schweinswurst, Berner Zungenwurst, Brianzola, Bierwurst, Emmentaler, Fleischkäse, Kümmelwurst, Lyoner (Aufschnittbrät), Tessiner Terrine, Schützenwurst, Frauenfelder Salzissen, Kalbsbratwurst, Cervelas, Knacker, St. Galler Kalbsbratwurst, St. Galler Stumpen, St. Galler Schüblig, Wienerli						

0 *) Based on http://www.abzspiez.ch/

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912 **[Fig. A. 1.]**

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914 **[Fig. A. 2.]**

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916 **[Fig. A. 3.]**

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918 **[Fig. A. 4.]**

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920 **[Fig. A. 5.]**

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922 **[Fig. A. 6.]**

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924 **Table A. 2.**

925 Sensitivity analyses of the hepatitis E foodborne risk assessment: Regression coefficients.

	Parameter	Pig Liver_cooked	Pâté au foie (Grundbrät)	Streich-leberwurst	Pâté de campagne	Terrine du Chef	Leberwurst Boudin blanc	Geflügel-fleisch-terrine	Hausmacher-leberwurst	Saucisse au foie_cooked
LOAD MODEL	HEV RNA load pig liver at slaughter	3.91	3.89	3.89	3.89	3.89	3.89	3.89	3.89	3.89
	Pasteurization effect	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45
	Mixing effect	n/a	4.84	4.84	4.84	4.84	4.84	4.84	4.84	4.84
WHOLE MODEL (Risk characterization)	Proportion acute illness(P_{ill})	225.73	347.16	328.14	414.64	414.64	125.04	275.82	237.78	89.88
	Proportion of exposed getting infected (P_{inf})	140.01	215.33	203.53	256.81	256.81	77.45	171.08	147.49	55.67
	Pig LIVER / HEV prevalence	52.20	80.28	75.88	69.31	69.31	20.90	63.78	54.98	15.02
	HEV Seroprevalence (Schnegg 2013)	33.00	50.75	47.97	61.18	61.18	18.45	40.32	34.76	13.26
	Pig MEAT / HEV prevalence	n/d	n/d	n/d	85,63	85,63	25.82	n/d	n/d	18.56

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928 **Table A. 3.**

929 Distribution of Hepatitis E cases in the Swiss canton of *Ticino* per year, sex and outcomes.

		Outcome 1 (hepatitis + GP visit)				Outcome 2 (hepatitis + hospitalization)			
		Number of cases	Number of deaths	Incidence rate (cases per 100,000 inhabitants)	Mortality rate (deaths per 100,000 inhabitants)	Number of cases	Number of deaths	Incidence rate (cases per 100 000 inhabitants)	Mortality rate (deaths per 100 000 inhabitants)
2010	Male	8	1	4.942	0.618	0	0	0.000	0.000
	Female	1	0	0.582	0.000	0	0	0.000	0.000
2011	Male	2	0	1.224	0.000	0	0	0.000	0.000
	Female	2	0	1.153	0.000	1	0	0.577	0.000
2012	Male	1	0	0.603	0.000	0	0	0.000	0.000
	Female	2	0	1.138	0.000	0	0	0.000	0.000
2013	Male	4	0	2.412	0.000	9	1	5.426	0.603
	Female	4	0	2.277	0.000	1	0	0.569	0.000
2014	Male	14	0	8.210	0.000	7	2	4.105	1.173
	Female	7	0	3.895	0.000	5	1	2.782	0.556
2015 (up to 01/09/15)	Male	29	2	17.007	1.173	7	0	4.105	0.000
	Female	10	0	5.565	0.000	5	2	2.782	1.113

930

931 One female patient was pregnant at the time of diagnostic; she recovered after hospitalization. Twelve patients had underlying chronic liver

932 diseases (e.g. alcoholic hepatitis, drug-induced hepatitis, hepatitis C or A) and 14 patients had no previous history of liver affections; the

933 information was missing for the remaining patients. Similarly, only sparse data was available on possible sources of infections. Eight patients
934 had not been abroad in the recent months, whereas six patients had; however, the assumption of a travel-related infection could not be
935 confirmed. Four patients reported regularly consuming different types of pork-products, such as fermented, cured or dried sausages, as well as
936 deer and wildboar meat, but no proper investigation was conducted to confirm foodborne infections. No information on food consumption
937 habits was available for the other patients.